

## Japanese encephalitis outbreak in India

The most serious outbreak of Japanese encephalitis (JE) in three decades has left nearly 800 dead and over 3500 infected in 30 districts across the state of Uttar Pradesh since July. More deaths have been reported in the adjoining state of Bihar. In Nepal—which shares an open border with Uttar Pradesh—259 people have died as a result of the mosquito-borne disease endemic in much of the paddy belt in Asia.

JE is transmitted by *Culex* mosquitoes that feed on domestic pigs and wild birds infected with the virus. Stagnant

water in areas of rice cultivation favours breeding of *Culex* mosquitoes. Symptoms of the JE include high fever, severe headaches, and convulsions; infection can lead to paralysis, coma, and death.

About a third of patients who recover from JE have residual neurological disability, including memory loss, impaired cognition, behavioural disturbances, convulsions, motor weakness or paralysis, and abnormalities of tone and coordination. However, these residual symptoms are not evident in the early stages and there is fear that the long-term consequences of JE will not get the attention they deserve in a state characterised by poverty, lack of education, and a public health-care system ill-equipped to deal with such a crisis. U K Mishra (Sanjay Gandhi Postgraduate Institute of Medical Sciences, Uttar Pradesh, India) says that a medical team of senior doctors from the institute, including himself, has visited Gorakhpur, the worst hit district, to collect data. The results of their neurological assessments are awaited.

“The biggest problem is insufficient follow-up”, says Lalitha Kabilan (Centre

for Research in Medical Entomology, Madurai, India). “In rural India, once a patient is discharged, he or she does not often go back to the doctor. My research showed that many children affected by JE were less than one year old when the disease struck them, and even their parents could not make out if they were suffering from neurological complications.”

Vaccination is the key preventive measure in the control of JE, along with better agricultural practices, including segregation of pig farms from human habitation. However, according to public health officials from the 15 Indian states where JE is endemic, India does not produce enough vaccine to meet local demand, and there is no common vaccine policy. WHO’s regional office has said that the Indian government has belatedly drawn up a plan for the next year, in which children age 1–12 years will be immunised against JE. However, as Kabilan says, more needs to be done by way of monitoring and assessing patients with JE across the country.

*Patralekha Chatterjee*

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Residual neurological deficits after JE infection may go un-noticed in children

## In search of the smallest infectious prion

The deposition of protein aggregates is a hallmark of many degenerative diseases, including Alzheimer’s, Parkinson’s, and prion diseases. The way in which deposits form and eventually kill neurons is unknown but, according to the results of a study by Byron Caughey and coauthors (Laboratory of Persistent Viral Diseases, NIH/NIAID, Hamilton, USA), small prion particles—not the fibrillar forms typically detected at autopsy—may trigger transmissible spongiform encephalopathies (TSEs). “Although the large prion protein aggregates tend to be more stable and easier to detect in infected tissues, smaller aggregates are the most infectious”,

explains Caughey, “therefore these data should influence efforts to detect TSE infections and decontaminate sources of TSE infectivity”.

The researchers fractionated by molecular size whole-brain samples from hamsters infected with scrapie (*Nature* 2005, **437**: 257–61). They then measured the infectivity associated with the different molecular sizes. “The smallest stable infectious unit contains at least six PrP molecules, so that its particle mass lies somewhere between 150–600 kDa”, Caughey told *The Lancet Neurology*. “Whether that particle mass is comprised entirely of PrP molecules or includes other unrecognised constituents remains to be determined”.

Martin Jeffrey (Veterinary Laboratories Agency, Midlothian, UK) comments “the study suggests that the most infectious fraction of a scrapie homogenate consists of circular or ellipsoidal aggregates of 14–28 prion molecules which are 20–25 nm in diameter”. However, he cautions, that “the size, shape, and infectivity of the particles within each fraction may not be exactly as PrP molecules are found in vivo”.

Charles Glabe (University of California, Irvine, USA) says “these results are strikingly similar to those obtained for other amyloid-related degenerative diseases, such as Alzheimer’s, Parkinson’s, Huntington’s

disease and type II diabetes, where intermediate sized oligomers have been reported to have a higher level of toxicity or pathogenic potential both *in vitro* and *in vivo*". Glabe adds that "treatments designed to break down amyloid fibrils may be counterproductive if they give rise to smaller oligomers that have increased infectivity".

According to Caughey, the study could have broad implications for therapeutic strategies: "Attempts to break up large aggregates such as amyloid plaques might cause more

harm than good. On the other hand, if one can reduce infectious aggregates to below a critical size, then the particles would lack the stability to survive *in vivo* as an infectious entity". Jeffrey supports this view: "My own observations of TSEs would suggest that full length amyloid, though damaging to tissues, is insufficient to result in clinical disease. No good data on the subcellular localisation of abnormal PrP in human diseases exists. Though some aggregates and amyloid in human diseases have been visualised other diseases do not show evidence of

visible amyloid. Thus amyloid or PrP aggregates cannot be the universal cause of neurological deficits."

Further studies are needed to clarify whether the small infectious particles cause disease progression and are a possible therapeutic target. "Treatment aimed at disaggregation of larger PrP fragments is illogical as the evidence already available does not support the role of fibrillar or aggregated PrP in pathological changes relating to clinical deficits", concludes Jeffrey.

*Elena Becker-Barroso*

## New mouse model with Down's syndrome phenotypes

Researchers in the UK have created a new animal model for Down's syndrome by inserting an almost complete copy of human chromosome 21 into the cells of mice. The creation of this transchromosomal mouse line is the most complete and closest model of the human syndrome (*Science* 2005; **309**: 2033–37).

Previous models have used either single-gene transgenics, which cannot model the complexity of Down's syndrome, or have used mice with partial chromosomal trisomies, says study author Elizabeth Fisher (Institute of Neurology, London, UK). "As human chromosome 21 is equivalent to several different chromosomes in mice, the mice with partial trisomies also cannot recreate the complexity of human Down's syndrome."

Down's syndrome—a common chromosomal defect—belongs to the class of disorders known as aneuploidies and develops as a result of an alteration in the number of wild-type genes on chromosome 21. Fisher and colleagues were able to manipulate mouse embryonic stem cells and insert a copy of human chromosome 21, thus generating a trans-species aneuploid mouse line. The transchromosomal mouse line that was created carries a chromosomal fragment with over 90% of the chromosome 21 genes.

"These trisomic mice have direct parallels with human trisomy 21 in effects on the growth and structure of neurons, craniofacial skeleton and skull, and even functional tests for hippocampus", comments Roger Reeves (Johns Hopkins School of Medicine, Baltimore, MD, USA). "The more comprehensive gene set in these mice produces an additional feature of Down's syndrome, congenital heart defects, that has not been seen in viable Down's syndrome's models previously, so the feasibility is unequivocally demonstrated here."

Fisher emphasises that the purpose of this research is not to "treat" Down's syndrome, but to provide an important tool in further understanding the complexities of this and other aneuploidies, which occur in at least 5% of all pregnancies.

People with Down's syndrome also have a higher susceptibility to disorders such as leukaemias, heart defects, and Alzheimer's disease, says Fisher, and this technology may be able to help researchers find out why.

Even though this is impressive work and represents a major accomplishment in making transchromosomal mice, Kathleen Gardiner (University of Denver, CO, USA) points out that this is merely another mouse model for Down's syndrome, and not a perfect

model. "The extra chromosome is not present in all cells, nor at the same frequency in all tissues, and will be variable from mouse to mouse", Gardiner comments. "This will most likely affect the phenotype."

"There is accumulating data that human and mouse genes frequently differ in their expression patterns and in alternative splicing", Gardiner adds. "Human genes in a mouse background are unlikely to express or function exactly like an extra human gene in a human would, or like a mouse gene would."

*Roxanne Nelson*

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Chromosome 21 triploidy in cells from a fetus with Down's syndrome